August 14, 2007 | vol. 104 | no. 33 | 13211–13532

PNAS

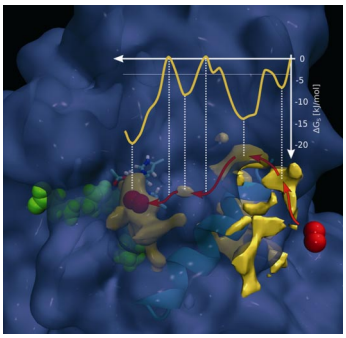
Proceedings of the National Academy of Sciences of the United States of America www.pnas.org

In This Issue

BIOPHYSICS

Oxygen diffuses into lipoxygenase via four channels

Molecular oxygen is critical to a number of physiological processes, including cellular respiration and eicosanoid formation. However, little is known about how dioxygen reaches enzyme active sites, which are often buried in the interior of proteins. Jan Saam *et al*. used a molecular dynamics approach, combined with site-directed mutagenesis and kinetic measurements, to study the diffusion of molecular oxygen in rabbit 12/15-lipoxygenase, a nonheme iron-containing fatty acid dioxygenase. They computed the three-dimensional free-energy distribution of oxygen in the enzyme, which revealed four distinct pathways by which dioxygen can diffuse from the protein surface into an area of high oxygen affinity at its active site. Formed by chains of mostly hydrophobic cavities, these channels are not continuously permeable but open and close transiently, governed by protein side-chain dynamics. The authors' methodology may be useful in other studies assessing the dynamics of gas diffusion in enzymes that utilize O_2, NO, CO, or CO_2. — F.A.



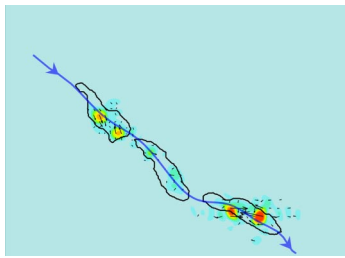
Free-energy distribution of oxygen in lipoxygenase.

"Molecular dioxygen enters the active site of 12/15-lipoxygenase via dynamic oxygen access channels" by Jan Saam, Igor Ivanov, Matthias Walther, Hermann-Georg Holzhütter, and Hartmut Kuhn (see pages 13319–13324)

CELL BIOLOGY

Cytometry method reveals *Dictyostelium* dynamics

Cellular motility is critical for a number of biological processes from embryogenesis and tissue growth to the proper function of the immune system. Juan del Álamo *et al*. have developed a force cytometry method that allows for high spatial and temporal resolution of cell movement and used this method to study the dynamics of *Dictyostelium discoideum* cell movement in a chemoattractant gradient. *Dictyostelium* amoebae exhibit many similarities to white blood cells, particularly neutrophils and macrophages. This cytometry method took into account the finite thickness of the deformable substrate on which the cells crawled as well as the distance between the measurement plane of the deformations and the surface of the substrate, unlike previous methods. The strain energy exerted by *Dictyostelium* cells during their motion is periodic, in accordance with the stages of the cell's motility cycle, and their velocity of migration is related to the period of the strain energy through a hyperbolic law, dependent on a constant step length. Álamo *et al*.'s work will aid in understanding the relationship between cellular motility and biological function. — F.A.



Composite image of a *D. discoideum* cell crawling on an elastic substrate.

"Spatio-temporal analysis of eukaryotic cell motility by improved force cytometry" by Juan C. del Álamo, Ruedi Meili, Baldomero Alonso-Latorre, Javier Rodríguez-Rodríguez, Alberto Aliseda, Richard A. Firtel, and Juan C. Lasheras (see pages 13343–13348)

MEDICAL SCIENCES

Clues to HIV protease inhibitors' side effects

Despite their success in dramatically reducing HIV blood titers and improving survival, most HIV protease inhibitors (HIV-PIs) have serious side effects, including metabolic syndrome, insulin resistance, increased blood lipid levels, and atherosclerosis. HIV-PIs were proposed to interfere with the biogenesis of lamin A, a protein that acts as part of the molecular scaffolding of the cell's nucleus. Interestingly, several mutations affecting lamin A biogenesis are associated with syndromes that exhibit features similar to the side effects of these drugs. To probe the molecular steps underlying HIV-PI-linked side effects, Catherine Coffinier *et al*. analyzed the processing of prelamin A, the precursor protein to lamin A, in cells exposed to HIV-PIs. Ex-

posure to physiological concentrations of HIV-PIs led to a significant accumulation of farnesylated prelamin A in cultured human and mouse cells. This accumulation was exaggerated in cells with half-normal levels of ZMPSTE24, an enzyme required for the conversion of prelamin A to mature lamin A. Several HIV-PIs were also found to inhibit ZMPSTE24 activity. The findings could facilitate the identification of new HIV-PIs that may have fewer side effects, as well as help identify individuals at the greatest risk for developing side effects from HIV-PIs, according to the authors. — M.M.

"HIV protease inhibitors block the zinc metalloproteinase ZMPSTE24 and lead to an accumulation of prelamin A in cells" by Catherine Coffinier, Sarah E. Hudon, Emily A. Farber, Sandy Y. Chang, Christine A. Hrycyna, Stephen G. Young, and Loren G. Fong (see pages 13432–13437)

MICROBIOLOGY, GEOLOGY

Ancient bacteria frozen in Antarctica

One theory for the origin of life on Earth suggests that microorganisms were delivered to the planet across interstellar space, frozen in comets. This scenario is unlikely, according to the results of a report from Bidle *et al.*, who analyze DNA from bacteria extracted from ancient ice in Antarctic glaciers. The authors carved blocks of ice from the Mullins and upper Beacon valleys of the Transantarctic Mountains. Ice crystal structure and isotopic analysis indicated that no melting had occurred since the original freezing, in the case of the oldest samples, for 8 million years. Spherical and filamentous shapes, apparently of bacteria, were visible in electron micrographs. The authors amplified the community DNA to examine 16S ribosomal DNA and found no exact matches with extant bacteria, although the majority of species showed high similarity. Even the most ancient bacteria were viable in liquid culture, if weakly so: their doubling time was >100 days. However, they could not be coaxed into forming colonies on agar plates. DNA gels revealed a high degree of fragmentation in the oldest genomes, caused by cosmic radiation unshielded at the South Pole. Comets would be subject to even stronger radiation, the authors say. — K.M.

Beacon Valley, Antarctica.

"Fossil genes and microbes in the oldest ice on Earth" by Kay D. Bidle, SangHoon Lee, David R. Marchant, and Paul G. Falkowski (see pages 13455–13460)